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(54) METHOD FOR PREPARING BLOOD PROCESSING DEVICE AND THE BLOOD PROCESSING DEVICE

(57)Abstract:
PURPOSE: To prevent a film from being deteriorated in the manufacturing process of a hollow fiber semipermeable membrane-type blood processing device and to provide a method for manufacturing a high performance blood processing device.
CONSTITUTION: By adhering the hollow fiber semipermeable membrane of a hollow fiber semipermeable membrane-type blood processing device with sodium chloride, an inorg. phosphate and a protective agent, it is possible to prevent a film from being deteriorated in a protective agent applying process and a radiation beam sterilizing process.

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CLAIMS

[Claim(s)]
[Claim 1] In the manufacture approach of a hollow fiber semipermeable membrane mold blood treater to this hollow fiber semipermeable membrane A sodium chloride, Make an inorganic-phosphoric-acid salt and a protective agent adhere, and a tubed container is loaded with the focusing object of this hollow fiber semipermeable membrane substantially made into dryness. After carrying out seal immobilization of the end with resin, cut an end at least and opening of the centrum of this hollow fiber semipermeable membrane is carried out. The manufacture approach of the hollow fiber semipermeable membrane mold blood treater characterized by carrying out radappertization where it assembled the blood treater and the inside of this blood treater is substantially held to dryness by attaching header material.
[Claim 2] The manufacture approach of the hollow fiber semipermeable membrane mold blood treater according to claim 1 which is what this hollow fiber semipermeable membrane becomes from 20% or more of cellulose acetate whenever [acetylation].
[Claim 3] The manufacture approach of a hollow fiber semipermeable membrane mold blood treater according to claim 1 or 2 that the total coating weight of a sodium chloride and an inorganic-phosphoric-acid salt is 0.1 - 2.0 % of the weight to the dry weight of only hollow fiber semipermeable membrane, and the presentation ratios (weight ratio) of a sodium chloride and an inorganic-phosphoric-acid salt are 50:50-95:5.
[Claim 4] The hollow fiber semipermeable membrane mold blood treater whose presentation ratios (weight ratio) of a sodium chloride and an inorganic-phosphoric-acid salt a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere to this hollow fiber semipermeable membrane, and the total coating weight of a sodium chloride and an inorganic-phosphoric-acid salt is 0.1 - 2.0 % of the weight to the dry weight of only hollow fiber semipermeable membrane in a hollow fiber semipermeable membrane mold blood treater, and are 50:50-95:5.
[Claim 5] The hollow fiber semipermeable membrane mold blood treater according to claim 4 which is what this hollow fiber semipermeable membrane becomes from 20% or more of cellulose acetate whenever [acetylation].
[Claim 6] The hollow fiber semipermeable membrane mold blood treater according to claim 4 or 5 which carried out radappertization.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the manufacture approach of the sterilized hollow fiber semipermeable membrane mold blood treater which is used for blood processing of hemodialysis, hemofiltration, plasma skimming, etc.
[0002]
[Description of the Prior Art] There is radiation sterilization as one of the sterilization approaches of a hollow fiber semipermeable membrane mold blood treater. When radappertization is used, that disassembly of the film material by the radiation and degradation arise poses a problem. For example, as for the extracted water solution, acidity is shown, when a film material is cellulose acetate and distilled water extracts, after carrying out radiation irradiation of the cellulose acetate hollow fiber semipermeable membrane which protected with the glycerol etc. by dryness substantially since it is easy to produce decomposition of the cellulose acetate by the radiation. Therefore, it consists of cellulose acetate hollow fiber semipermeable membrane, when a priming is carried out with a physiological saline before using the blood treater which performed radiation irradiation sterilization by dryness substantially, the liquid shows acidity and has the danger that acid priming liquid will go into the inside of the body if washing is inadequate, and the cure is required. For example, a buffer is made for JP,2-88074,A to adhere to hollow fiber semipermeable membrane with a protective agent (plasticizer), and the approach of carrying out gamma irradiation sterilization by dryness substantially is indicated. It is possible to stop that the extract after radiation irradiation becomes acidity by this approach.
[0003] However, while pH of the solution containing protective agents, such as a buffer and a glycerol, presents alkalinity and produces decomposition and film degradation of cellulose acetate in this process at the process which makes protective agents, such as a buffer and a glycerol, adhere to cellulose acetate hollow fiber semipermeable membrane by this approach, the part is changed into a cellulose, the fall of whenever [acetylation] is caused, the fall of membrane permeability ability, such as protein by change of membranous surface charge, takes place, and it is not desirable.
[0004]
[Problem(s) to be Solved by the Invention] The invention in this application prevents decomposition at an adhesion process and film degradation of the protective agent to the hollow fiber semipermeable membrane which is a trouble on the conventional blood treater manufacture in the first place, prevents decomposition and degradation of souring of the priming liquid after a radappertization process and the film further, and aims at raising the engine performance of a blood treater.
[0005]
[Means for Solving the Problem] this invention person found out reducing pH of a processing solution by adding the sodium chloride whose thing to which this processing mixed solution was presenting alkalinity to the hollow fiber semipermeable membrane front face in adhesion down stream processing of a buffer and a protective agent is the neutral salt considered not to influence pH of this solution at all conventionally, as a result of inquiring wholeheartedly for the purpose of canceling this conventional trouble. By carrying out adhesion processing of a sodium chloride and an inorganic-phosphoric-acid salt to adhesion processing of a protective agent and coincidence in the hollow fiber before loading the

tubed container for blood treaters by this Decomposition of the cellulose acetate which is the material of the hollow fiber semipermeable membrane in protective agent adhesion processes, such as a buffer and a glycerol, Find out that film degradation can be controlled and the fall of whenever [acetylation / which is the index] can be controlled, and it is further set to radappertization down stream processing. It became possible to give radappertization to hollow fiber semipermeable membrane, where dryness is held substantially, and a header and this invention were reached [also having the film degradation prevention effectiveness and].

[0006] In the manufacture approach of a hollow fiber semipermeable membrane mold blood treater that this invention was sterilized A sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent are made to adhere to this hollow fiber semipermeable membrane. And a tubed container is loaded with the focusing object of this hollow fiber semipermeable membrane substantially made into dryness. Resin cuts an end for an end at least after seal immobilization, and opening of the centrum of this hollow fiber semipermeable membrane is carried out. By attaching header material, a blood treater is assembled and the manufacture approach of the hollow fiber semipermeable membrane mold blood treater characterized by carrying out radappertization where the inside of this blood treater is substantially held to dryness is offered.

[0007] Hereafter, this invention is further explained to a detail.

[0008] The hollow fiber semipermeable membrane concerning this invention consists of a material which may generate an acid by radiation irradiation, such as a gamma ray, and cellulose ester, polymethylmethacrylate, etc. are mentioned. In the case of the hollow fiber semipermeable membrane which consists of 20% or more of cellulose acetate whenever [acetylation], especially this invention is effective, and if it is 30 - 61% of range whenever [acetylation] also in it, there will be little degradation by radiation irradiation and it will become more advantageously applicable. Whenever [acetylation] shows the amount of association of the acetic acid occupied in a polymer by the weight %, and means whenever [average acetylation] here.

[0009] The inorganic-phosphoric-acid salt in this invention is not limited especially if the purpose can be attained, and as the example, things further depended on such combination, such as calcium hydrogenphosphate monobasic, tribasic potassium phosphate, phosphoric-acid 3 sodium, dibasic potassium phosphate, disodium hydrogen-phosphate, potassium dihydrogen phosphate, and sodium dihydrogen phosphate, are mentioned. As a desirable thing, disodium hydrogen-phosphate is especially mentioned in these.

[0010] As the total coating weight of a sodium chloride and an inorganic-phosphoric-acid salt, 0.1 - 1.5 % of the weight is especially desirable 0.1 to 2.0% of the weight to the dry weight of only hollow fiber semipermeable membrane. In this range, there is an advantage which is easy to prevent the poor seal depended on that the film degradation prevention effectiveness after sterilization is acquired certainly and coincidence badly [adhesion of hollow fiber semipermeable membrane and the resin for seals]. If the total coating weight exceeds 2.0 % of the weight, a sodium chloride and an inorganic-phosphoric-acid salt will deposit at the time of desiccation, and the seal immobilization by resin will become difficult by adhering to a hollow fiber semipermeable membrane front face superfluously. Conversely, the total coating weight has the trouble which cannot prevent pH of the extract after sterilization becoming acidity easily at less than 0.1%.

[0011] As a presentation ratio (weight ratio) of a sodium chloride and an inorganic-phosphoric-acid salt, the range of 50:50-95:5, especially 80:20-95:5 is desirable. In this range, while preventing that pH of the extract after sterilization becomes acidity, there is an advantage which is easy to prevent that pH of this mixed solution becomes alkalinity at the process which makes a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere to hollow fiber semipermeable membrane.

[0012] The protective agent in this invention is made to adhere in order to prevent membraneous ability falls, such as protection of the pore of the film when making hollow fiber semipermeable membrane into dryness substantially, and water permeability, its polyhydric alcohol, such as a glycerol and a polyethylene glycol, etc. is desirable, and its glycerol is desirable also especially in them. The proper range of the coating weight to the hollow fiber semipermeable membrane of this protective agent changes with classes of semipermeable membrane, and is determined by the saturation coating weight from the comparatively low permeable membrane of the pore void content to a plasma

demarcation membrane with a high void content. The condition of having permuted and filled up with all of the pore sections in the film here with the protective agent is in a saturation adhesion condition, and the protective agent coating weight at that time is saturation coating weight. It is under saturation-on parenchyma coating weight, the desirable coating weight of the protective agent in this invention has 40 - 300 still more preferably desirable % of the weight to the dry weight of hollow fiber semipermeable membrane, and its 50 - 200 % of the weight is especially desirable. It may be difficult for this coating weight to avoid degradation of the film at the time of film degradation by the radiation, and desiccation, such as water permeability, at less than 40 % of the weight. Moreover, when a protective agent is made to adhere more than saturation coating weight, the hollow internal surface or outside surface of hollow fiber semipermeable membrane may be dotted with a superfluous protective agent liquid drop-like, and seal immobilization with hollow fiber semipermeable membrane and resin may become difficult. So, 300 % of the weight is mentioned as an upper limit of the range where protective agent coating weight is desirable.

[0013] In this invention, after making a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere to hollow fiber semipermeable membrane, and not being limited especially as an approach of making it into dryness substantially, and making the sodium chloride of predetermined concentration, an inorganic-phosphoric-acid salt, and the mixed water solution of a protective agent adhere to hollow fiber semipermeable membrane, for example, removing an excessive water solution with an air knife, the approach of fully drying in hot blast is mentioned. It is desirable from the point that it tends to ensure growth prevention of a bacillus that it is the amount which does not reach the condition that substantial dryness here means that extent which a bacillus cannot usually increase easily is dry, and moisture exists in [of an in / the membranous wall of hollow fiber semipermeable membrane / whole] pore especially. Moreover, when manufacturing hollow fiber semipermeable membrane by approaches, such as wet spinning using a core agent, after washing a core agent, it is desirable to make a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere.

[0014] The sodium chloride, inorganic-phosphoric-acid salt which were obtained by doing in this way in this invention, And make a protective agent adhere and the tubed container for blood treaters is made to load with the focusing object of this hollow fiber semipermeable membrane substantially made into dryness. After carrying out the seal of the both ends by centrifugal molding etc. using resin, such as urethane resin or an epoxy resin, A blood treater is assembled by cutting with the resin which fixed the hollow fiber semipermeable membrane of an end at least, carrying out opening of the centrum of hollow fiber semipermeable membrane, and making the header material for distributing blood etc. to the opening further fix. In this invention, after putting into bags, such as polyethylene and polyester, and sealing, holding the interior to dryness substantially in this blood treater, sterilization processing is performed by irradiating radiations, such as a gamma ray. The range of 15-50kGy is [that what is necessary is just the range where the sterilization effectiveness is acquired without having a bad influence on the member which constitutes blood treaters, such as hollow fiber semipermeable membrane, as an exposure of a radiation] desirable.

[0015]

[Example] This invention is not limited by them although the example of this invention is shown with the example of a comparison below.

[0016] [An example 1 and an example 2]

- Heating fusion of the mixture which consists of the flakes of the examination-cellulose diacetate (average degree of polymerization: whenever [260 and acetylation] 53.8%) of the total coating weight of a sodium chloride and disodium hydrogen-phosphate, a polyethylene glycol (mean molecular weight 400), diglycerol, and 1,4-butanediol was carried out, it extruded from the outer tube of a double pipe nozzle, nitrogen gas was rolled round from the inner tube by part for discharge and 200m/to coincidence as a core material, and the hollow fiber original film with a bore [of 200 micrometers] and an outer diameter of 230 micrometers was obtained. The superfluous glycerol which carried out immersion processing of this original film for 30 seconds at the 80-degree C hot bath, and adhered to the 55-% of the weight glycerol mixed water solution of a sodium chloride and disodium hydrogen-phosphate after immersion for 1 minute continuously at the film outside surface was dried by removal and hot blast by the compressed air, and the hollow fiber semipermeable membrane of cellulose diacetate was obtained. At this time, by changing the concentration of the water solution of a sodium

chloride and disodium hydrogen-phosphate like a following table publication, the total coating weight of the sodium chloride and disodium hydrogen-phosphate to the weight of only the hollow fiber semipermeable membrane after desiccation was prepared so that it might become about 1.0 % of the weight (= example 1) and about 0.3 % of the weight (= example 2). Whenever [acetylation / of the cellulose diacetate which is pH of the mixed solution at this time and the index of film degradation] was shown in Table 1. After containing what cut the semipermeable membrane of this hollow fiber semipermeable membrane in die length of 27cm in the tubed case of polycarbonate resin in the about 12,000 bundle and drying, polyurethane resin cut both ends after immobilization, header material was attached further, and the hemodialyzer was assembled. Then, it sealed into the polyethylene bag and packed up in the carton case. The gamma ray of 22kG(ies) was irradiated in this condition, and sterilization processing was performed. 150ml of distilled water is added to 1.5g of things which cut hollow fiber semipermeable membrane to about 2cm after an exposure, and it warms for 1 hour and let 70 degrees C be test fluid. As a result of measuring pH of the solution which added 1ml of potassium chloride water solutions of the concentration of 1 g/L to this test fluid and 20ml of each used distilled water and computing pH difference (deltapH) of both liquid, the result of Table 1 was obtained. On dialysis mold hemodialysis apparatus acknowledgement criteria, it is required for this deltapH to be less than 1.5, and 1.5 or more are not desirable as a blood treater.

[0017] Consequently, pH of a sodium chloride, disodium hydrogen-phosphate, and the mixed water solution of a glycerol became the eight neighborhoods, decomposition of cellulose diacetate and film degradation were suppressed, and reduction which is whenever [acetylation] was controlled. Moreover, pH difference was also in criteria.

[0018]

[Table 1]

	NaCl濃度 (重量%)	Na_2HPO_4濃度 (重量%)	NaCl・Na_2HPO_4 総付着量 (重量%)	混合水溶液 pH(50℃)	酢化度	ΔpH	備考
実施例1	0.87	0.13	1.04	8.19	53.51	1.03	
実施例2	0.261	0.039	0.28	8.13	53.46	1.32	
比較例1	0	0.3	0.28	8.73	52.00	1.22	
比較例2	0	0	0	6.84	53.68	1.66	
比較例3	0.087	0.013	0.06	8.16	53.53	1.50	
比較例4	2.01	0.30	2.34	8.17	53.50	0.39	ウレタン部の接着不良発生

[0019] Although deltapH was in criteria as a result of processing by the glycerol water-solution bath whose disodium hydrogen-phosphate concentration is 0.3% at the process which processes the cellulose-diacetate hollow fiber semipermeable membrane in the 55-% of the weight glycerol mixed water solution bath in the [example 1 of comparison] example 1, whenever [acetylation] was decreasing and decomposition of cellulose diacetate and film degradation arose.
[0020] Although whenever [acetylation] was not different from the flakes of a raw material and decomposition of cellulose diacetate and film degradation did not break out at the process which processes the cellulose-diacetate hollow fiber semipermeable membrane in the 55-% of the weight glycerol mixed water solution bath in the [example 2 of comparison] example 1 as a result of processing by the glycerol water-solution bath containing neither a sodium chloride nor disodium hydrogen-phosphate, deltapH brought a result besides criteria.
[0021] At the process which processes cellulose-diacetate hollow fiber semipermeable membrane by the 55-% of the weight glycerol mixed water solution bath of the [example 3 of comparison] example 1, the concentration of a sodium chloride and disodium hydrogen-phosphate was changed so that the sodium chloride and disodium hydrogen-phosphate total coating weight might become 0.1 % of the weight, and the blood treater was obtained. consequently, the sodium chloride and disodium hydrogen-phosphate total coating weight -- this application -- although decomposition of cellulose diacetate and film degradation at least did not take place rather than a claim, deltapH was outside criteria highly.

[0022] At the process which processes cellulose-diacetate hollow fiber semipermeable membrane by the 55-% of the weight glycerol mixed water solution bath of the [example 4 of comparison] example 1, the concentration of a sodium chloride and disodium hydrogen-phosphate was changed so that the sodium chloride and disodium hydrogen-phosphate total coating weight might become 2.3 % of the weight, and the blood treater was obtained. Consequently, although pH of a sodium chloride and the mixed water solution of disodium hydrogen-phosphate addition fell and film degradation was suppressed, the adhesive agent of urethane resin and hollow fiber semipermeable membrane occurred.
[0023] About the blood treater of [example 3] example 1 and example of comparison 1 publication, path clearance measurement was performed and the result of Table 2 was obtained. Path clearance measurement passed the amount of hollow filament inlet-port side streams by part for part [for /], and 200ml outlet side flow rate/of 192ml, using 0.2 g/L water solution of a dextran (mean molecular weight 10,000) or alpha-lactalbumin, a myoglobin, and the 0.1 g/L phosphoric-acid buffer solution (NaCl 9 g/L, Na2HPO4 37.7 g/L, KH2PO4 7.9 g/L) of Cytochrome C as a blood side solution. Ion exchange water was poured by part for 500ml/instead of dialysing fluid in the tubed case to it and coincidence. Measurement was carried out at 37 degrees C. It asked for path clearance (CL:ml/min) by the degree type.
[0024] The cable address in a CL=(QBixCBi-QBoxCBo)/CBi top type is as follows.
CBi: Entrance-side concentration of a blood side solution (g/L)
CBo: Outlet side concentration of a blood side solution (g/L)
QBi: The amount of inlet-port side streams of a blood side solution (a part for g/)
QBo: The outlet side flow rate of a blood side solution (a part for g/)
[0025] The path clearance of alpha-lactalbumin whose path clearance of the dextran which are a result and a saccharide is protein although a difference is not accepted in the blood treater of example 1 and example of comparison 1 publication, a myoglobin, and Cytochrome C improved sharply in the blood treater of an example 1.
[0026]
[Table 2]

	酢化度	クリアランス (ml/min)			
		ﾃﾞｷｽﾄﾗﾝ	α-ﾗｸﾄｱﾙﾌﾞﾐﾝ	ﾐｵｸﾞﾛﾋﾞﾝ	ﾁﾄｸﾛｰﾑC
実施例1	53.51	21	45	42	36
比較例1	52.00	21	38	33	30

[0027]
[Effect of the Invention] According to the manufacture approach of the blood treater of this invention, the priming liquid at the time of carrying out a priming with a physiological saline before use can be defanged, and the blood treater excellent in safety can be offered. Moreover, since decomposition of cellulose acetate and film degradation are prevented and whenever [acetylation] can be held highly, the fall of the membrane permeability ability of the protein accompanying change of membranous surface charge can be prevented. Furthermore, growth of the bacillus within the blood treater before sterilization is prevented, and a blood treater without a pyrogen is obtained easily.

[Translation done.]